

REMARKS

Entry of the foregoing, reexamination and reconsideration of the application identified in caption, as amended, pursuant to and consistent with 37 C.F.R. §1.111 and in light of the remarks which follow, are respectfully requested.

By the above amendments, the instant specification has been amended to recite the §371 date of parent Application No. 09/254,598, as well as the corresponding issued patent number. The specification at page 1 has also been amended for readability purposes by deleting the word "in" prior to "on."

Claim 7 has been amended for clarification purposes by deleting the terms "transferrin" and "albumin," as well as by deleting the section (b) of the claim. In light of such amendment, claim 7 is now directed to a conjugate of a cytostatic compound and a polyethylene glycol. Claim 10 has been amended for readability purposes by deleting the comma after the word "wherein." Claims 10 and 11 have been amended for clarification in accordance with the above amendments of claim 7.

In the Official Action at page 2, the specification stands objected to for reciting that the filing date of parent Application No. 09/254,598 is March 11, 1999. The Patent Office has indicated that the correct filing date of the parent application is May 21, 1999. However, Applicant submits that the parent application was indeed filed on March 11, 1999, and the date on which the requirements under 35 U.S.C. §371 were met is May 21, 1999. In an effort to expedite prosecution, and in compliance with the Examiner's request, the specification has been amended to recite the §371 date of May 21, 1999. Accordingly, withdrawal of this objection is respectfully requested.

Claim 10 stands objected to for reciting a comma after the word "wherein." Claim 10 has been amended for readability purposes by deleting such comma. Accordingly, withdrawal of this objection is now in order.

Claims 7-14 stand rejected under the judicially created doctrine of obviousness-type double patenting as being obvious over claims 1-9 of U.S. Patent No. 6,310,039. It is respectfully requested that this rejection be held in abeyance until the Patent Office provides indication that the pending claims are allowable over the applied art of record.

Claims 7-9 stand rejected under 35 U.S.C. §102(a) as being anticipated by European Journal of Pharmaceutical Sciences, Vol. 4, Suppl. 1996 (*Beyer et al*). Claims 12 and 13 stand rejected under 35 U.S.C. §103(a) as being obvious over *Beyer et al*. Withdrawal of these rejections is respectfully requested for at least the following reasons.

According to one aspect of the present invention as defined by claim 7, a conjugate of a cytostatic compound and a polyethylene glycol is provided. The cytostatic compound is coupled via a spacer comprising a group which is derived from a maleinimido group, to polyethylene glycol having at least one HS or H₂N group. The polyethylene glycol has a mass of about between 5,000 and 200,000 Da.

Beyer et al does not disclose or suggest each feature of one aspect of the present invention as defined by claim 7. For example, *Beyer et al* does not disclose or suggest a cytostatic compound which is coupled via a spacer comprising a group which is derived from a maleinimido group, to polyethylene glycol having at least one HS or H₂N group. By comparison, *Beyer et al* discloses attaching cytotoxic drugs to "the carrier proteins, human serum transferrin and albumin." There is simply no disclosure of a cytostatic compound which is

coupled to polyethylene glycol, let alone polyethylene glycol having at least one HS or H₂N group. And certainly, *Beyer et al* has no disclosure or suggestion that such polyethylene glycol has a mass of about between 5,000 and 200,000 Da.

For at least the above reasons, it is apparent that *Beyer et al* does not anticipate or render *prima facie* obvious the presently claimed invention. Accordingly, withdrawal of the above rejections is respectfully requested.

Claims 7 and 10-13 stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,208,021 (*Johnson et al*). Claims 7-13 stand rejected under 35 U.S.C. §103(a) as being obvious over *Johnson et al*, and further in view of Journal of Bioactive and Compatible Polymers, Vol. 9, July 1994 (*Nathan et al*). Withdrawal of the above rejections is respectfully requested.

Johnson et al relates to cancer and chemotherapy and, more particularly, to a reagent which selectively kills cancer cells and can be used to treat graft versus host disease (col. 1, lines 11-14). *Johnson et al* discloses preparing an immunotoxin by coupling inactivated diphtheria toxin to a binding moiety such as a monoclonal antibody or transferrin (See abstract).

Johnson et al does not disclose or suggest each feature of one aspect of the present invention as defined by claim 7. For example, *Johnson et al* fails to disclose or suggest a cytostatic compound which is coupled via a spacer comprising a group which is derived from a maleinimido group, to polyethylene glycol having at least one HS or H₂N group, as recited in claim 7. By comparison, *Johnson et al* discloses mixing an MBS-conjugated toxin with thiolated transferrin (col. 12, lines 43-46). However, there is no disclosure or suggestion of a cytostatic

compound which is coupled to polyethylene glycol having at least one HS or H₂N group, let alone that such polyethylene glycol has a mass of about between 5,000 and 200,000 Da.

Nathan et al as applied by the Patent Office fails to cure the above-described deficiency of *Johnson et al*. In this regard, the Patent Office has relied upon *Nathan et al* for disclosing the use of doxorubicin (Official Action at page 5). The Patent Office has asserted that it would have been obvious to substitute the doxorubicin disclosed by *Nathan et al* with the diphtheria toxin in the conjugates of *Johnson et al*.

Assuming *arguendo* that such substitution would have been obvious and feasible, Applicant notes that the conjugate resulting from such substitution would have been a conjugate of a diphtheria toxin and transferrin. Clearly, such alleged conjugate would not have been the same as or suggestive of the recited cytostatic compound which is coupled via a spacer comprising a group which is derived from a maleinimido group, to polyethylene glycol having at least one HS or H₂N group.

For at least the above reasons, it is apparent that the alleged combination of *Johnson et al* and *Nathan et al* does not render the presently claimed invention *prima facie* obvious. Accordingly, withdrawal of the above rejections is respectfully requested.

Claims 7-13 stand rejected under 35 U.S.C. §103(a) as being obvious over *Johnson et al* in view of *Nathan et al*, and further in view of *Beyer et al* or U.S. Patent No. 5,622,929 (*Willner et al*). Claims 7-13 stand rejected under 35 U.S.C. §103(a) as being obvious over *Johnson et al* in view of *Nathan et al*, and further in view of U.S. Patent No. 4,980,457 (*Jansen et al*). The deficiencies of *Johnson et al*, *Nathan et al* and *Beyer et al* are discussed above. For example, such documents as applied by the Patent Office fail to disclose or suggest a cytostatic compound

which is coupled via a spacer comprising a group which is derived from a maleinimido group, to polyethylene glycol having at least one HS or H₂N group, as recited in claim 7.

Willner et al and *Jansen et al* fail to cure the above-described deficiency of the above documents. In this regard, the Patent Office has relied on *Willner et al* for disclosing that in the conjugate arts it is routine to substitute one known drug for another while maintaining the same spacers and carriers/targeting agents (Official Action at page 6). *Jansen et al* has been relied upon for disclosing conjugates containing aliphatic spacing structures (Official Action at page 6). However, *Willner et al* and *Jansen et al* fail to disclose or suggest a cytostatic compound which is coupled via a spacer comprising a group which is derived from a maleinimido group, to polyethylene glycol having at least one HS or H₂N group, as recited in claim 7.

For at least the reasons discussed above, it is apparent that no *prima facie* case of obviousness exists. Accordingly, withdrawal of the §103(a) rejections is respectfully requested.

Claims 7-13 stand rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,030,620 (*Hannart et al*) in view of U.S. Patent No. 5,705,363 (*Imakawa*). Withdrawal of this rejection is respectfully requested for at least the following reasons.

Hannart et al relates to conjugates of vinca alkaloids of the indole-dihydroindole type with proteins or protein fragments which are endowed with pharmaceutical properties (col. 1, lines 8-11). *Hannart et al* discloses that the proteins which can be used are bovine or human serum albumin, or fetuin or immunoglobulins (col. 4, lines 33-35).

Hannart et al fails to disclose each feature of one aspect of the present invention as defined by claim 7. For example, *Hannart et al* fails to disclose or suggest a cytostatic compound which is coupled via a spacer comprising a group which is derived from a

maleinimido group, to polyethylene glycol having at least one HS or H₂N group, as recited in claim 7. In stark contrast with the present invention, *Hannart et al* discloses the use of bovine or human serum albumin, or fetuin or immunoglobulins. There is simply no disclosure or suggestion of the recited polyethylene glycol having at least one HS or H₂N group. And certainly, *Hannart et al* fails to disclose or suggest that such polyethylene glycol has a mass of about between 5,000 and 200,000 Da.

The Patent Office has relied on *Imakawa* for curing a deficiency of *Hannart et al* by disclosing that albumin can be thiolated for use in forming conjugates (Official Action at page 7). However, like *Hannart et al*, *Imakawa* does not disclose or suggest a cytostatic compound which is coupled via a spacer comprising a group which is derived from a maleinimido group, to polyethylene glycol having at least one HS or H₂N group, as recited in claim 7.

For at least the above reasons, it is apparent that no *prima facie* case of obviousness exists. Accordingly, withdrawal of the rejection based on *Hannart et al* and *Imakawa* is respectfully requested.

Claims 7 and 11-13 stand rejected under 35 U.S.C. §103(a) as being obvious over Photochemistry and Photobiology, Vol. 58, No. 5 (*Motsenbocker et al*). Claim 14 stands rejected under 35 U.S.C. §103(a) as being obvious over *Motsenbocker et al*, and further in view of *Hannart et al*. Withdrawal of these rejections is respectfully requested for at least the following reasons.

Motsenbocker et al relates to the synthesis of methylene blue derivatives having a succinimido or maleimido functional group and the coupling thereof to antibody, serum albumin and transferrin proteins (See abstract).

Motsenbocker et al does not disclose or suggest each feature of one aspect of the present invention as defined by claim 7. For example, *Motsenbocker et al* does not disclose or suggest a cytostatic compound which is coupled via a spacer comprising a group which is derived from a maleinimido group, to polyethylene glycol having at least one HS or H₂N group, as recited in claim 7. Rather, as discussed above, *Motsenbocker et al* discloses coupling methylene blue derivatives to antibody, serum albumin and transferrin proteins. There is simply no disclosure or suggestion of a cytostatic compound which is coupled to polyethylene glycol, let alone polyethylene glycol having at least one HS or H₂N group. As well, *Motsenbocker et al* fails to disclose or suggest that such polyethylene glycol has a mass of about between 5,000 and 200,000 Da.

Hannart et al fails to cure this deficiency of *Motsenbocker et al*. In this regard, as mentioned above in the discussion regarding the §103(a) rejection based on *Hannart et al* and *Imakawa*, *Hannart et al* does not disclose or suggest a cytostatic compound which is coupled via a spacer comprising a group which is derived from a maleinimido group, to polyethylene glycol having at least one HS or H₂N group.

As such, it is apparent that no *prima facie* case of obviousness exists. Accordingly, withdrawal of the above rejections is respectfully requested.

Claims 7-10, 12 and 13 stand rejected under 35 U.S.C. §102(a) as being anticipated by Bioorganic and Medicinal Chemistry Letters, Vol. 7, No. 5, 1997 (*Kratz et al*). Withdrawal of this rejection is respectfully requested for at least the following reasons.

Kratz et al relates to binding maleimide groups to the 3'-amino position of daunorubicin through a benzamide bond or to the 13-keto position through a benzoyl hydrazone or phenylacetyl hydrazone bond (See abstract).

Kratz et al does not disclose each feature of one aspect of the present invention as defined by claim 7. For example, *Kratz et al* does not disclose a cytostatic compound which is coupled via a spacer comprising a group which is derived from a maleinimido group, to polyethylene glycol having at least one HS or H₂N group, as recited in claim 7. By comparison, *Kratz et al* discloses the development of daunorubicin conjugates of the serum protein transferrin, and has no disclosure of the use of polyethylene glycol having at least one HS or H₂N group in the formation of a conjugate (page 617, second paragraph). And certainly, *Kratz et al* fails to disclose that such polyethylene glycol has a mass of about between 5,000 and 200,000 Da.

For at least the above reasons, it is apparent that *Kratz et al* does not anticipate the presently claimed invention. Accordingly, withdrawal of the §102(a) rejection is respectfully requested.

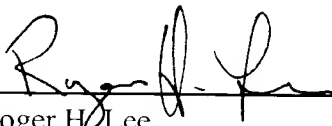
From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

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If there are any questions concerning this paper or the application in general, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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